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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,813	04/13/2007	**Ulrich Bogdahn**	JCLA21512	6647

23900 7590 08/11/2009

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
08/11/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,813	BOGDAHN ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-21 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *March 27, 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission mailed on June 19, 2009 has been entered.

Claims 22, 24, and 25 have been canceled. Claims 19-21, and 23 have been amended.

Claims 19-21, and 23 are pending in the instant application.

Claims 19-21, and 23 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Applicant's information disclosure statement filed March 27, 2009 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Nucleotide Sequence Disclosures

In the previous Office Action mailed April 1, 2009, it was noted that the instant application failed to comply with the requirements of 37 C.F.R. §1.821-1.825 because pages 13, 17, and 36 of Applicant's disclosure contained sequences which fall under the purview of 37 CFR 1.821 through 1.825 as requiring SEQ ID NOs., but which are not so identified.

Response to Arguments

In response to this notice, Applicants state in their Response filed June 19, 2009 at page 10 of 14:

> "Please find enclosed a new Sequence Listing in both computer readable form (CRF) and paper copy"

However, it does not appear that a new Sequence Listing has been made of record. In fact, on Applicant's Transmittal Sheet filed with the Response on June 19, 2009, it does not appear that Applicants even submitted a new Sequence Listing as stated.

In this regard, the instant application still fails to comply with the sequence requirements of 37 C.F.R. §1.821-1.825. Applicant must fully comply with the requirements of 37 C.F.R. §1.821-1.825 for any response to this action to be considered fully responsive.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed April 1, 2009, claims 19-25 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly

point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is moot** against claims 22, 24, and 25 in view of Applicant's Amendment filed June 19, 2009 to cancel these claims. **This rejection is withdrawn** against claims 19-21, and 23 in view of Applicant's Amendment filed June 19, 2009. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to remove language reciting the recitation of a use.

Claim Rejections - 35 USC § 101

In the previous Office Action mailed November 7, 2008, claims 19-25 were rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. **This rejection is moot** against claims 22, 24, and 25 in view of Applicant's Amendment filed June 19, 2009 to cancel these claims. **This rejection is withdrawn** against claims 19-21, and 23 in view of Applicant's Amendment filed June 19, 2009. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to remove language reciting the recitation of a use.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed November 7, 2008, claims 19-25 were rejected under 35 USC 102(b) as being anticipated by WO 03/000656 A2. **This rejection is moot** against claims 22, 24, and 25 in view of Applicant's Amendment filed

June 19, 2009 to cancel these claims. **This rejection is withdrawn** against claims 19-21, and 23 in view of Applicant's Arguments filed June 19, 2009. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Arguments that WO 03/000656 (also referred to as "Murray") does not teach a method for promoting regeneration and functional reconnection of damaged neural pathways by administering TGF-βRII antisense oligonucleotides as now claimed. It should be noted that WO 03/000656 primarily teaches that the TGF-βRII antisense oligonucleotides of their invention are used in methods of treating cancerous diseases and conditions that involve the activation of the immune system.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-21, and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a method of promoting successful regeneration and functional reconnection of damaged neural pathways in a mammal, comprising the direct or local administration of a therapeutically effect amount of SEQ ID NO:3, does not reasonably provide enablement for a method of promoting successful regeneration and functional reconnection of damaged neural pathways in a mammal, comprising administering a therapeutically effective amount of least one oligonucleotide having a sequence at least 80% identical to a sub-sequence of SEQ ID NO:1, comprising 8 to 50

nucleobases, wherein said sequence is capable of hybridizing sufficiently with the region encompassing the translation initiation or termination codon of the open reading frame of the gene encoding TGF-R_{II} or a region of the mRNA encoding TGF-R_{II} which is a "loop" or "bulge" and which is not part of a secondary structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims. This is a scope enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The instant claims are drawn to a method of promoting successful regeneration and functional reconnection of damaged neural pathways in a mammal, comprising administering a therapeutically effective amount of least one oligonucleotide having a sequence at least 80% identical to a sub-sequence of SEQ ID NO:1, comprising 8 to 50 nucleobases, wherein said sequence is capable of hybridizing sufficiently with the

region encompassing the translation initiation or termination codon of the open reading frame of the gene encoding TGF-R_{II} or a region of the mRNA encoding TGF-R_{II} which is a "loop" or "bulge" and which is not part of a secondary structure. The broadness of the methods recited in the claims implies *in vivo* applicability of any oligonucleotide therapeutic targeted to TGF-βRII including antisense, ribozymes, triplex, and siRNA for enablement purposes. The nature of the invention, therefore, requires the knowledge of using oligonucleotide therapeutics that can be delivered to cells or tissues in mammal such that regeneration and functional reconnection of damaged neural pathways are successfully promoted.

The amount of direction or guidance and presence/absence of working examples:

Applicants have disclosed only one TGF-βRII antisense oligonucleotide that functions in a method of promoting successful regeneration and functional reconnection of damaged neural pathways in a mammal as claimed. It is noted that Applicants have disclosed that such a method is carried out when the antisense oligonucleotide is administered locally (e.g. local delivery to the brain). See Examples 6-8, for example.

The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the claimed methods in *in vivo* environments using any/all oligonucleotide therapeutics targeted to TGF-βRII. Additionally, a person skilled in the art would recognize that predicting the efficacy of a compound, particularly an oligonucleotide therapeutic *in vivo* is unpredictable. Thus, although the specification discloses a method of promoting successful regeneration and functional reconnection of damaged neural pathways in a mammal, comprising the

direct or local administration of a therapeutically effect amount of SEQ ID NO:3, such a disclosure would not be considered enabling for any/all oligonucleotide therapeutics targeted to TGF-βRII or for any/all modes of delivery since the state of the art of oligonucleotide-mediated gene inhibition in living organisms is highly unpredictable.

The state of the prior art and the predictability or unpredictability of the art:

The claimed invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001). The following references are cited herein to illustrate the state of the art of delivery of oligonucleotide therapeutics into targeted cells, tissues, and organs *in vivo*:

Ogorelkova et al. (Oligonucleotides, 2006 Vol. 16:2-14) teach that regarding the use of antisense RNA and short hairpin RNA for silencing TGF-βRII expression, antisense RNA were ineffective in silencing endogenous TGF-βRII. Ogorelkova et al. also teach:

> "The enduring challenge is to identify molecules that specifically and optimally silence a given target gene"; and
>
> "The fact remains that not all antisense RNAs designed against a particular target have an antisense effect, and selection of efficient antisense RNAs is largely a matter of trial and error"

The level of skill in the art:

The relative skill of those in the art is considered to be high, being a graduate student or post-doctoral fellow in a biological science.

The quantity of experimentation necessary:

A review of the instant application finds adequate guidance for a method of promoting successful regeneration and functional reconnection of damaged neural pathways in a mammal, comprising the direct or local administration of a therapeutically effect amount of SEQ ID NO:3. Although, Applicants clearly recognize the potential of using other oligonucleotide therapeutics targeted to TGF-βRII in a method of promoting successful regeneration and functional reconnection of damaged neural pathways in a mammal, Applicants only teach the ordinary artisan how to effectively deliver SEQ ID NO:3 to a mammalian subject. No technical guidance or exemplary disclosure is provided regarding the mode of delivery of any other oligonucleotide therapeutic, as the claims broadly encompass the use of antisense, ribozymes, triplex, and siRNA. As the reference above indicates, oligonucleotide therapeutics into targeted cells, tissues, and organs *in vivo* is highly unpredictable.

Thus, it is maintained that the prior art at the time of Applicant's filing would not enable the disclosure of one TGF-βRII antisense oligonucleotide in a method of promoting successful regeneration and functional reconnection of damaged neural pathways in a mammal to support claims directed to methods of using any/all oligonucleotide therapeutics targeted to TGF-βRII for use in a method of promoting successful regeneration and functional reconnection of damaged neural pathways in a subject. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification enough to overcome the

unpredictability and challenges of applying results for the local delivery of SEQ ID NO:3 to delivery of any/all oligonucleotide therapeutics targeted to TGF-βRII, as exemplified in the references above.

In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of those oligonucleotide therapeutics targeted to TGF-βRII, other than SEQ ID NO:3, that promote successful regeneration and functional reconnection of damaged neural pathways in a subject. Since the specification fails to provide any real guidance for methods of using any/all oligonucleotide therapeutics targeted to TGF-βRII *in vivo*, other than SEQ ID NO:3, and since resolution of the various complications in regards to targeting a particular gene in a living organism is unpredictable, one of skill in the art would have been unable to practice the invention, commensurate in scope with the claims, without engaging in undue trial and error experimentation.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached from 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's

supervisor, James "Doug" Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Terra Cotta Gibbs/
August 8, 2009